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Japanese Encephalitis

*Japanese B Encephalitis,
Arbovirus B,
Mosquito-borne Encephalitis Virus*

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Importance

Japanese encephalitis virus (JEV) is a mosquito-borne agent that can cause encephalitis in equids and humans and reproductive disease in pigs. Rare clinical cases have also been reported in other species, such as cattle. Japanese encephalitis can be a very serious disease in people: although most infections are asymptomatic, clinical cases tend to manifest as severe encephalitis, and many survivors are left with neurological sequelae. All ages can be affected in a population without previous exposure; however, Japanese encephalitis tends to be a childhood disease in endemic areas, where most people develop immunity by the time they reach adulthood. Morbidity and mortality can be high in unvaccinated populations during epidemics. Approximately 4,000 people died during the 1924 epidemic in Japan, and nearly 2500 fatalities occurred in South Korea in 1949. Likewise, more than 3700 equids died during an epidemic in Japan in 1949.

Japanese encephalitis virus has gradually expanded its geographic range within Asia and spread to parts of the western Pacific region during the last 50 years. It could become endemic in additional regions, similarly to West Nile virus, which became established in the Americas in the 1990s. Eradication is unlikely once JEV enters mosquito populations, as the virus is maintained and amplified in cycles between these vectors and various vertebrate hosts such as pigs and wild birds. Vaccination has reduced the number of clinical cases among horses in endemic areas, and is mandatory in certain animals (e.g., racehorses) in some countries. Childhood vaccination has, likewise, greatly decreased the number of human cases in some nations; however, vaccination rates vary, and this disease is still very common in some areas. Some regions have recently reported a relative increase in the percentage of cases seen in adults, leading to suggestions that vaccination campaigns also be conducted in this group.

Etiology

Japanese encephalitis virus (JEV) is an arbovirus (arthropod-transmitted virus) in the genus *Flavivirus* and family *Flaviviridae*. There is only one serotype of JEV, but at least five genotypes. Some genotypes are more common than others, and the dominant genotypes in an area can change over time. For example, genotype I has become common in some areas where genotype III used to be prevalent.

Japanese encephalitis virus is closely related to St. Louis encephalitis virus, Murray Valley encephalitis virus and West Nile virus; these viruses and a few others comprise the Japanese encephalitis serogroup of the flaviviruses.

Species Affected

Illnesses caused by JEV occur mainly in equids (e.g., horses, donkeys) and pigs; however, rare clinical cases have been reported in cows, and other species may be susceptible. Asymptomatic infections have been documented in many other domesticated and wild mammals (e.g., cattle, sheep, goats, rabbits, dogs, cats, wild boar, raccoons) and birds, as well as in reptiles and amphibians. Reports of infections in some species may be based on serology alone.

Ardeid birds (herons and egrets) and suids (domesticated and wild pigs) develop viremia sufficient to infect mosquitoes, and are considered to be important in maintaining and amplifying JEV. Other birds (e.g., young poultry, swallows) have also been suggested as possible reservoirs, and many avian species have never been examined for their ability to maintain or amplify this virus. There are also reports suggesting that bats might be significant in some cycles. An early study suggested that wild rodents are not important maintenance hosts.

Zoonotic potential

Humans are susceptible to Japanese encephalitis.

Geographic Distribution

Japanese encephalitis is widespread in temperate and tropical regions of Asia, and also occurs in parts of the western Pacific. Its precise distribution in some areas is unclear, due to limited surveillance and/or cross-reactivity with other flaviviruses in

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serological tests. In Australia, the virus is endemic on the Torres Strait islands, and there have been reports of it on the northern mainland, but it may not be established in the latter location. There are also rare reports describing possible JEV in mosquitoes and birds in southern Europe. Specifically, a portion of the JEV genome was identified in dead birds in Italy in 2000, and JEV gene segments were detected by PCR in mosquitoes in Italy in 2010. However, the evidence to date is not definitive, and the presence of circulating live virus remains to be confirmed.

Transmission

Japanese encephalitis virus is usually transmitted by mosquitoes in the genus *Culex*. The specific mosquito vectors vary with the region; however, *Culex tritaeniorhynchus* is important in spreading this virus to humans and domesticated animals across a wide geographic range. *C. tritaeniorhynchus* breeds in rice paddies and connecting canals, and is active at twilight. Other culicine species can also be important locally and/or as minor vectors. For example, members of the *C. sitiens* subgroup, especially *C. annulirostris*, are the most important vectors in Australia. JEV has been reported in other genera of mosquitoes, and it was isolated from *Culicoides* midges in China, but the significance of these vectors is unclear.

JEV is usually transmitted in mosquito bites, although lizards and bats can also become infected by eating infected mosquitoes. Humans and most domesticated animals are incidental hosts, with low viremia, and are not considered to be important in virus transmission. For example, while horse-to-horse transmission via mosquitoes has been demonstrated in the laboratory, viremia is low and there are usually too few susceptible horses nearby to maintain the virus. Although both birds and suids can amplify JEV, domesticated pigs are considered to be particularly good amplifying hosts, as large numbers of susceptible young swine are produced each year, sometimes in close proximity to people. Boars are reported to transmit the virus in semen.

In addition to mosquito bites, infections in people have been reported after exposure to JEV in the laboratory or during tissue sample collection. This virus can be transmitted through mucous membranes or broken skin, inhaled in aerosols, or acquired by needlestick injuries.

Japanese encephalitis virus does not survive well outside a living host. How the virus persists during the winter in temperate climates is uncertain, although various mechanisms have been suggested.

Disinfection

Agents reported to be effective for JEV disinfection include 70% ethanol, 2% glutaraldehyde, 3–8% formaldehyde, 1% sodium hypochlorite, iodine, phenol iodophors and organic solvents/detergents. This virus is also sensitive to heat, ultraviolet light and gamma irradiation.

Infections in Animals

Incubation Period

The incubation period in experimentally infected horses is 4 to 14 days. Experimentally infected pigs can develop clinical signs after 3 days (with rising temperature detected in some animals as early as 24 hours after inoculation).

Clinical Signs

Most infections in horses are subclinical, and symptomatic cases vary in severity. Some horses have a mild illness with nonspecific signs such as a transient fever, anorexia, lethargy, and congested or jaundiced mucous membranes. This syndrome usually lasts for 2–3 days, and the horse recovers without complications. Other horses develop encephalitis. In the milder form, the animal is lethargic and anorexic, with a fluctuating fever and neurological signs that commonly include difficulty swallowing, incoordination, transient neck rigidity, radial paralysis or impaired vision. Signs of jaundice or petechial hemorrhages may be found on the mucous membranes. These horses often recover within a week. A more severe but uncommon form, called the “hyperexcitable form,” is characterized by high fever, aimless wandering, violent and demented behavior, profuse sweating, muscle tremors and occasionally blindness. Although some horses with this form recover, many collapse and die in 1–2 days. Neurological defects such as ataxia may persist in some animals after recovery.

Naive pigs may have reproductive signs. The most common syndrome in this species is the birth of stillborn or mummified fetuses, usually at term. Infected piglets born alive often have tremors and convulsions, and die soon after birth. Pregnant sows may also abort. Nonpregnant pigs usually remain asymptomatic or experience a transient febrile illness, but signs of encephalitis are occasionally seen in pigs up to six months of age. A wasting syndrome was reported in one group of piglets with post-mortem evidence of nonsuppurative meningoencephalitis. In addition, disturbances of spermatogenesis can cause infertility in boars. Although this is usually temporary, it can be permanent in severely affected animals.

Other domesticated animals can be infected but typically remain asymptomatic. Rare cases of Japanese encephalitis in cattle were characterized by neurological signs, sometimes preceded by nonspecific signs (e.g., fever, depression, decreased appetite). Some of these cases were fatal; other animals were euthanized. Three experimentally infected dogs did not develop clinical signs, and the authors of this study reported that no clinical cases have been seen among dogs in Japan, even during epidemics in other species.

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Post Mortem Lesions [Click to view images](#)

Only nonspecific lesions are seen in horses, and there are no characteristic gross lesions in the brain. Diffuse nonsuppurative encephalomyelitis is the characteristic microscopic lesion. Nonsuppurative encephalitis was also reported in the few cattle reported to have Japanese encephalitis, but the macroscopic lesions varied. One animal had no gross lesions in the brain, spinal cord or other organs. In two other cases, hemorrhages and/or congestion were found in the brain. Additional lesions with uncertain relevance to Japanese encephalitis were reported in some cases, and included pulmonary emphysema in two cattle.

Mummified or stillborn fetuses can be found in litters from infected sows. Congenital neurological defects including hydrocephalus, cerebellar hypoplasia and spinal hypomyelination may be seen in some litters. Experimentally infected piglets with encephalitis had swelling and edema of the brain.

Diagnostic Tests

A definitive diagnosis of Japanese encephalitis can be made by virus isolation. Isolating JEV from infected horses can be difficult, even from tissues collected at necropsy; however, it may be attempted from brain samples (e.g., corpus striatum, cortex or thalamus) and the spinal cord. Tissue samples should be very fresh, i.e., taken from animals that have been dead for less than 12 hours, or from animals killed during the acute stage of the disease. It may also be possible to isolate this virus from the blood, serum or CSF of living horses, but viremia is usually short-lived and this is rarely successful. In swine, JEV may be isolated from the brains of affected fetuses or piglets with encephalitis. The sow has usually cleared the virus by the time an affected litter is born. Various cell lines are suitable for virus isolation; some culture systems that have been used include chicken embryo, baby hamster kidney (BHK) cells, African green monkey kidney (Vero) cells, the MDBK cell line and mosquito cell lines (e.g. C3/36). Mouse inoculation is also used during virus isolation. JEV can be recognized as a flavivirus by hemagglutination inhibition or enzyme-linked immunosorbent assays (ELISAs), and its identity can be confirmed by virus neutralization, reverse transcription polymerase chain reaction (RT-PCR) assays, or immunofluorescence to detect viral antigens.

JEV can also be detected directly in tissues or blood by RT-PCR; however, there is little published information on the use of this technique with clinical samples. Immunohistochemistry has been used to identify viral antigens in the central nervous system (CNS). Histopathology is also helpful.

Serology is often used to diagnose Japanese encephalitis in endemic regions. Serological diagnosis can be complicated by pre-existing antibodies from vaccination or previous exposure to JEV, or cross-reactive antibodies to other viruses in the Japanese encephalitis serogroup. Tests that may be available include virus neutralization (e.g., the plaque

neutralization test), hemagglutination inhibition, ELISAs to detect IgM (IgM capture ELISA) or IgG, and less commonly used assays such as complement fixation. Virus neutralization is the most specific assay, and has low cross-reactivity, but its availability may be limited. In endemic regions, a definitive serological diagnosis usually depends on a significant rise in titer with paired acute and convalescent samples. Sows usually seroconvert before the onset of reproductive signs, and rising titers may not be observed in these animals. A presumptive diagnosis may be made if a high titer is found in a single serum sample and supportive evidence suggests Japanese encephalitis. In horses, the detection of specific IgM and IgG in cerebrospinal fluid (CSF) is also good evidence of infection.

Treatment

There is no specific antiviral therapy for Japanese encephalitis. Affected animals are treated symptomatically. Infected animals may be euthanized in regions where this disease is not endemic.

Control

Disease reporting

Veterinarians who encounter or suspect a Japanese virus infection should follow their national and/or local guidelines for disease reporting. In the U.S., state or federal authorities must be notified immediately.

Prevention

Japanese encephalitis vaccines can prevent disease in horses and pigs in endemic areas. Sows are widely vaccinated for Japanese encephalitis in some countries, but not in others. Maternal antibodies may interfere with vaccination during the short lifespan of young pigs. Although vaccines are cross-protective between viral genotypes, some reports suggest their relative efficacy might differ. Past vaccines generally contained genotype III viruses, but new genotype I vaccines are being developed in some areas where these viruses have become common, and may soon be commercially available. Various measures to reduce contact with mosquitoes, such as stabling animals in screened barns during peak mosquito biting activity, can be partially protective, particularly during outbreaks. Insecticide-treated mosquito nets have sometimes been used to help protect pigs. Environmental control of mosquitoes may temporarily help control these vectors during an outbreak, but large-scale use of insecticides is costly, difficult to implement well long-term, may have adverse effects on the environment, and is impractical in many areas.

Some control measures in swine are intended to help reduce the risk to other species. For example, pigs are sometimes relocated away from human population centers. Because JEV is also maintained in birds, some transmission can be expected to continue even if virus amplification in pigs can be controlled.

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Morbidity and Mortality

Japanese encephalitis may be a seasonal disease in endemic areas, depending on factors such as climate and rainfall patterns. In temperate regions, it may peak among horses in late summer and autumn when the virus spills over after being amplified in pigs and other animals. JEV circulates year-round in tropical areas, but there may be seasonal peaks of disease associated with irrigation, rainfall or other factors that affect the local abundance of mosquitoes and vertebrate amplifying hosts. In some areas, epidemics are associated with the rainy season.

In horses, cases usually occur sporadically or in small clusters, but epidemics may be seen when there are large numbers of susceptible animals. Inapparent infections are common in this species. Between 1948 and 1967, the morbidity rate in Asia was estimated to be approximately 0.045% (45 cases per 100,000 horses), but higher morbidity rates were reported during some outbreaks. During the 1948 epizootic in Japan, the morbidity rate in horses was 0.3% overall, and as high as 1.4% in some areas. The case fatality rate in horses is reported to be approximately 5% or less in some areas, and 5-15% in others. Case fatality rates as high as 30-40% have been reported in some outbreaks. For example, when one group of susceptible broodmares was introduced to an endemic area, a third of the mares died. Vaccination has reduced the incidence of clinical cases among horses in endemic regions.

Naïve pigs are reported to be highly susceptible to infection, with pregnant sows often aborting or giving birth to stillborn and mummified fetuses. During one epidemic in Japan, 50-70% of all pigs suffered reproductive losses. Affected piglets born alive often die; however, the mortality rate is close to zero in adult pigs. Japanese encephalitis may have much less impact on pigs in endemic regions, where they can develop immunity by the time they are bred. In one recent study, the only effects on reproductive performance occurred in young sows (i.e., animals <1.5 years of age), and there was no impact when sows of all ages were analyzed. The number of swine in a region may affect the incidence of disease in other species, due to virus amplification in these animals. However, this varies with the type of husbandry practices, and modern pig farming does not necessarily increase the risk of infection. Where Japanese encephalitis is seasonal, serological surveillance in pigs can be used to help predict epidemics in humans. Some researchers have also suggested using serology in dogs, which are infected asymptotically, to help predict human risk.

Infections in Humans

Incubation Period

The incubation period in humans is estimated to be 5 to 15 days.

Clinical Signs

The initial signs of Japanese encephalitis are usually nonspecific; they may include fever, chills, muscle aches and severe headache with vomiting. Children may appear to have a gastrointestinal illness, with nausea, vomiting and abdominal pain. Coryza and diarrhea are also mentioned by some authors. Some people recover after this stage, but others develop neurological signs. Signs suggestive of benign aseptic meningitis occur in a minority of the latter group, but most patients with neurological signs have encephalitis. Signs of encephalitis may develop gradually after the initial, nonspecific illness, or as a sudden onset of fever and convulsions. They may include a reduced level of consciousness, which can progress to coma; focal neurological signs; quadriplegia, hemiplegia or cerebellar disorders; and behavioral changes. Painful stiffness of the neck, and mild to severe convulsions, ranging from subtle focal signs to generalized seizures, are common. Movement disorders also occur frequently, and some people develop transient Parkinson's like signs (e.g., masking of the face, paucity of blinking, rigidity with or without tremor, akinesia). Various atypical presentations have been reported, and include isolated acute onset behavioral abnormalities that may be misdiagnosed as psychiatric illnesses. Occasionally patients can develop flaccid paralysis resembling polio; some of these patients may not have signs of encephalitis. Some case series also describe syndromes in other organs, such as pulmonary edema and upper gastrointestinal hemorrhage.

Convalescence can be prolonged, although some patients make a rapid, spontaneous recovery ("abortive encephalitis"). Up to 50% of the survivors have neurological sequelae such as epileptic seizures, a Parkinsonian syndrome with tremors and rigidity, or cognitive, behavioral or language impairment. Some survivors gradually improve, although this can take months or years. Miscarriages have been seen in pregnant women who were infected for the first time during pregnancy; however, this is reported to be uncommon in endemic areas.

Diagnostic Tests

Serology is often used to diagnose Japanese encephalitis in endemic areas, typically by detecting IgM in acute phase serum and CSF with an ELISA. Some studies have reported that a few patients were seronegative in serum, CSF or both. Asymptomatic infections or vaccination usually result in the presence of IgM in the serum but not CSF. Cross-reactivity with other flaviviruses is an issue in some serological assays such as ELISAs and hemagglutination inhibition. Virus neutralization tests can also be used, and a fourfold rise in neutralizing antibody titer is diagnostic in retrospective cases.

Viremia in humans is usually transient and low level, and direct detection of viruses in the blood by virus isolation and/or RT-PCR is reported to be difficult. RT-

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PCR may also detect viral RNA in the CSF; however, this method does not appear to be commonly employed.

Neuroimaging and electroencephalographic analysis can also be helpful, although they are not definitive.

Treatment

Treatment is supportive. There are currently no specific antiviral therapies for this disease.

Control

Several vaccines are available for humans. Japanese encephalitis vaccines are cross-protective against all viral genotypes; however, there are reports that immunity against genotypes other than the vaccine strain may be weaker. Childhood vaccination is routine in some countries. With a relative increase in adult cases, some areas are also considering or conducting vaccination campaigns in adults. In non-endemic areas, vaccines are primarily given to laboratory workers at risk of infection and travelers to endemic region. Recommendations for the latter group vary, depending on factors such as the season, duration of travel, activities and lodging.

Other temporary preventive measures include the use of insect repellents, insecticide-impregnated bed nets, and long-sleeved shirts and pants to discourage mosquito bites. Environmental modifications to decrease mosquito populations (e.g., intermittent irrigation of rice fields, larvivorous fish, insecticide spraying) may be used in some areas or situations. Approaches to reduce amplification in pigs, as described above (Infections in Animals), have also been suggested or implemented.

Morbidity and Mortality

Japanese encephalitis is an important cause of illness, death and disability in parts of Asia. Vaccination, changes in agricultural practices, improved standards of living and other factors have greatly reduced the incidence of this disease in some countries; however, it continues to be widespread in others. More than 27,000 cases were reported to the World Health Organization (WHO) between 2006 and 2009, and one recent analysis estimated the true worldwide incidence to be approximately 68,000 cases per year. As in animals, the patterns of disease in endemic regions vary with factors such as climate and rainfall. Human illnesses, like those in horses, may peak in late summer and autumn in some temperate regions, but can occur year-round in the tropics, with seasonal peaks caused by local factors such as rainfall.

The risk of developing encephalitis is affected by many factors including the person's age and immunity to flaviviruses. All ages can be affected in a population without previous exposure; however, clinical cases mainly occur in children (< 15 years) in endemic regions, where people usually develop immunity by the time they reach adulthood. An increasing proportion of cases have been reported in adults in some areas where children are

vaccinated. The risk of infection also tends to be higher in rural areas than cities. Most human infections are asymptomatic: studies from endemic regions estimate that approximately one in every 100 to 1,000 infected people develops clinical signs. During some outbreaks (e.g., in people from nonendemic regions), this ratio can be as high as 1 in 25. The risk to all travelers visiting endemic regions has been estimated to be < 1 case per 1 million; however, the specific risk varies with the season, duration of travel, activities and lodgings. While most cases occur in people who visit an endemic area for a longer time, clinical cases have also occurred in short-term travelers.

In symptomatic cases, reported case fatality rates range from < 5% to 40% and are occasionally higher. Some countries have reported that case fatality rates as well as morbidity rates have decreased significantly in recent years, possibly due to partial immunity from an incomplete vaccination series, better care and/or other factors. Up to 30-50% of survivors have mild to severe neurological sequelae. Some of these people gradually improve, although this can take months or years.

Internet Resources

Centers for Disease Control and Prevention (CDC) Japanese Encephalitis Home Page

<http://www.cdc.gov/japaneseencephalitis/>

Public Health Agency of Canada. Pathogen Safety Data Sheets

<http://www.phac-aspc.gc.ca/lab-bio/res/psds-ftss/index-eng.php>

The Merck Veterinary Manual

<http://www.merckvetmanual.com/mvm/index.html>

United States Animal Health Association. Foreign Animal Diseases

http://www.aphis.usda.gov/emergency_response/download/nahems/fad.pdf

World Organization for Animal Health (OIE)

<http://www.oie.int>

OIE Manual of Diagnostic Tests and Vaccines for Terrestrial Animals

<http://www.oie.int/international-standard-setting/terrestrial-manual/access-online/>

OIE Terrestrial Animal Health Code

<http://www.oie.int/international-standard-setting/terrestrial-code/access-online/>

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